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PATENTS

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Applicant(s): Juan C. Colberg et al.

Examiner: M. Berch

Serial No: 10/006,279

Art Unit: 1624

Filed: December 4, 2001

Docket: PC10862A (15905)

For: COUPLING PROCESS AND INTERMEDIATES USEFUL FOR PREPARING CEPHALOSPORINS

Dated: August 11, 2003

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. §1.113

Sir:

This is in response to the Official Action dated April 11, 2003.

All but four of the claims submitted for examination in this application have been finally rejected on substantive grounds. Applicants have considered the rejection of record and respectfully submit that all the claims submitted for examination in this application

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CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

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Dated: August 11, 2003

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are patentable thereover.

It is noted at the outset that Claims 12 and 17-20 stand objected to as being dependent upon a rejected base claim. However, the Official Action states that these claims would be allowable if rewritten in independent form to include all the limitations of the base claim and any intervening claims. The Official Action thus admits to the patentable subject matter of Claims 12 and 17-20. These claims remain in the application.

The reason why the aforementioned claims have not been rewritten in independent form, to place these claims in condition for allowance, is because applicants respectfully traverse the rejection of Claims 1-11, 13-16 and 20-24, which stand rejected, under 35 U.S.C. §103(a), as being unpatentable over International Publication IP No. WO 92/01696 to Bateson et al.

It is unnecessary to review the extensive remarks included in the outstanding Official Action in support of the proposition that Claims 1-11, 13-16 and 20-24 are made obvious, under 35 U.S.C. §103(a), by Bateson et al. Suffice it to say, the Official Action admits that the acylation step in Bateson, e.g. Example 1, step g, occurs by reaction of compounds II and III where compound II is an ester. In the claims subject to this ground of rejection the compound II is an acid. The Official Action challenges applicants to show unexpected effects arising from the use of an acid rather than the prior art teaching of an ester.

Applicants meet this challenge. Attention is directed to step (g) in Example 1 of Bateson et al. Therein mesyl chloride is reacted with 2-(Z)-methoxyimino-2-(2-tritylaminothiazol-4-yl) acetic acid hydrochloride and N, N-diisopropylethylamine. This reaction, is conducted in dimethylformamide (DMF), at cryogenic temperature, that is, -40°C. This product, in turn, is reacted with the ester, t-butyl (6R, 7R)-7-amino-3-(tetrahydrofuran-2-

yl)ceph-3-em-4-carboxylate, and diastereroisomer, in DMF, followed by pyridine. This reaction occurs at –30±°C. That is, the second reaction also occurs under cryogenic conditions. Although step (g) of Example 1 in Bateson et al. does not recite atmospheric conditions, the atmosphere for this reaction is an inert gas.

On the other hand, the equivalent processing step in the present invention, utilizing an acid, involves reaction of a compound, within the scope of compound II in Claim 1, 7-amino-8-oxo-3-(tertrahydrofuran-2-yl)-5-thia-1-aza-bicyclo[4.2.0]octa-1(6), 2,4-triene-2-carboxylic acid in the presence of a compound within the scope of formula III in Claim 1, a mixture of (Z)-2-amino-α-(methoxyamino)-4-thiazoleacetic acid anhydride and O, O-diethyl hydrogenphosphorothioate.

This synthesis step, in accordance with Claim 1 of the present application, is set forth in Example 1, Method A, at page 27 of the instant specification. It is emphasized that the mixture of the acid anhydride and phosphorothioate is a commercially available product. This reaction occurs in the presence of water and at atmospheric temperature.

The distinction set forth in the above remarks meets the requirement imposed in the outstanding Official Action. That is, unexpected results are obtained utilizing the process of the present application compared to that disclosed in the prior art Bateson et al. disclosure.

Those skilled in the art appreciate that the necessity of cryogenic conditions in conducting the reaction of step (g) in Bateson et al. is because mesyl chloride is a highly unstable compound which hydrolyzes upon contact with moisture. Clearly, the processing steps of the claimed invention of the present application, as exemplified in Example 1, Method A, which is conducted in the presence of water, could not be conducted in the presence of mesyl chloride.

Those skilled in the art are furthermore aware of the unstable nature of the reaction product of the ester reactant and the Bateson et al. equivalent of applicants' compound III. It is because of the unstable nature of mesyl chloride and reaction products thereof that necessitates the utilization of cryogenic temperatures of between -20°C and -40°C as well as inert atmospheric conditions to produce the same compounds.

The above remarks emphasize the unexpected results obtained by the Official Action admitted distinction between the process of the present application and that of Bateson et al. Clearly, the process of the present application, utilizing an acid as compound II, permits commercial production of commercially important cephalosporins which prompted the invention of the present application over the process disclosed in Bateson et al.

If further evidence is necessary to establish the unexpected result obtained by the process of Claims 1-11, 13-16 and 20-24 over that disclosed in Bateson et al. one need merely appreciate that the assignee of the applied Bateson et al. and present application are now identical. That a new process would be devised to produce this commercially important class of compounds emphasizes the need in the art for a process that is far more easy to commercially practice than is the process taught in the applied Bateson et al. disclosure.

It is noted that the aforementioned unexpected reactivity obtained by the utilization of an acid, rather than an ester, in the process of the present application, as discussed above, is implicitly admitted in the Official Action by the observation that there is no claim language limiting the process to non-cryogenic temperatures.

Applicants respectfully urge that the language of the claims of the present application does not necessitate any additional limitations to distinguish over the Bateson et al. process. The clear line of distinction between compound II, which is an acid, in Claim 1, compared to

the Bateson et al. ester infers this temperature distinction. Those skilled in the art are aware that the Bateson et al. ester must be reacted under cryogenic temperatures in order for the reaction to go forward. The inclusion of temperature distinction in the process claims of the present application is thus deemed unnecessary and unduly restrictive.

The further Official Action statement, regarding the absence of any discussion in Bateson et al. of temperature requirements, in the specification at Pages 17 and 18, is of no consequence insofar as the working examples establish that cryogenic temperatures are indeed required, as discussed above.

Even if the other Bateson et al. examples were conducted in an ice bath, such a disclosure would still emphasize, to one skilled in the art, the difficulty of reacting mesyl chloride and the resulting instability of the product of such reaction. As indicated in the working examples of the present application, extremely low temperatures, to permit reaction with the far more inert esters in Bateson et al., are not utilized in the production of cephalosporins in accordance with the utilization of the acid of compound II in the claimed process of the present application.

Turning to the product claims, Claims 21-24, these claims are not disclosed by Bateson et al. The aforementioned remarks, which establish the improved processing of cephalosporins using these intermediate compounds, establish unobviousness, under 35 U.S.C. §103(a). It is only through the use of the compounds of Claims 21-24 that the improved process of the present application can be conducted. As such, these admittedly new compounds possess an unexpected result not disclosed or suggested by the applied Bateson et al. reference.

Reconsideration and removal of the substantive rejection of record is therefore deemed appropriate. Such action is respectfully urged.

The above remarks establish the patentable nature of all the claims currently in this application. Notice of Allowance and passage to issue of these claims, Claims 1-24, is therefore respectfully solicited.

Respectfully submitted,

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